Remarks/Arguments

The present amendment amends claims 1, 4-9, 33-35, 38-44, 46 and 49; and adds new claims 55-64. The amendment is without prejudice to future prosecution.

Support for the amendment is provided in application. Examples of support include the descriptions of percent identical and amino acid alterations on page on page 12, line 33 to page 13, line 1, and page 14, lines 6-11; reference to adjuvant on page 20, lines 1-17; and references to COL on page 7, line 34 to page 8, line 11.

Reference in the amendment to the immunogen providing protective immunity against COL is a functional property of the immunogen and is not method step or a limitation as to how the immunogen is used. The pending claims are directed to the compounds and compositions and are not limited to any particular use.

Enclosed with the present response is an IDS that includes a press release referencing V710. V710 is an experimental vaccine corresponding to ORF0657nI.

35 U.S.C. § 102: Claims 1, 4, 7, 33 and 49

Claims 1, 4, 7, 33 and 49 stand rejected as allegedly anticipated under 35 U.S.C. § 102 as evidenced by "*Opposition against European Patent No. 1651166 in the name of Merck Sharp & Dogme Corp.* – Applicants' IDS)" and Applicants admitted state of the prior art. As described below, claims 1, 4, 7, 33, and 49 were amended to further describe the invention.

Roche *et al.,* is cited for allegedly teaching the suitability of LPXTG-anchored surface proteins for vaccine development. The Examiner takes the position the *Roche et al.,* SasJ48-477 fragment has at least 94% identity with the instantly recited SEQ ID NO: 3 and the fragment has at least 94% identity with SEQ ID NO: 1. The Examiner also alleges Applicants have acknowledged the Roche *et al.,* fragment shares at least 94% identity to SEQ ID NO: 1, and goes to assert:

> Therefore, if the prior art teaches the identical chemical structure, the properties Applicants disclose in the specification and/or claims, i.e., provide protective immunity against *S. aureus,* or the capacity to be an immunogen as defined at line 25 page 2 of Applicants' specification, are necessarily present.

Office Action dated 4/13/2011 at page 4.)

The rejection fails to indicate where the prior art describes a SasJ polypeptide having a 94% identity to SEQ ID NO: 3, and incorrectly asserts Applicants have admitted the Roche *et al.,* polypeptide fragment containing 48-477 of SasJ (ORF0645) shares at least 94% amino acid identity with SEQ ID NO: 1. Applicants also note the opposition provided in the prior IDS was against "Merck Sharp & Dohme Corp", not "Merck Sharp and Dogme Corp", as indicted by the Examiner, and assumes the Examiner's reference to "SasJ (ORF0645)" is intended to mean SasJ (ORF0657n). Applicants response to the opposition is included in the IDS submitted with the present amendment.

The Examiner's reference to the SasJ 48-477 fragment sharing at least 94% amino acid identity with SEQ ID NO: 1 appears to be based on the assumption of a 100% identical sequence in the overlapping region between SEQ ID NO: 1 and SasJ 48-477 fragment. (See Exhibit A attached hereto.)

The failure of Roche *et al*. to provide the SasJ 48-477 sequence, prevents analysis as to whether there is 100% identity. ORF0657 sequences can vary among different species of *S. aureus.* This is highlighted in the sequences provided in Figures 2A-2E of the present application. Thus, it cannot be assumed the Roche *et al.* SasJ fragment shares a region with 100% sequence identity to SEQ ID NO 1.

As further discussed in the response to the § 103 rejection *infra.* Roche *et al.,* fails to provide any teaching leading the skilled artisan to a reasonable expectation of success using SasJ as an protective antigen. The Examiner's point concerning compounds within the scope of the rejection claims being expected to inherently have the ability to provide productive immunity is noted. Applicants have amended the claims to exclude the Roche *et al.,* SasJ 48-477 fragment, even assuming the fragment shares 100% identical sequence in the overlapping region with SEQ ID NO: 1.

35 U.S.C. § 103: Claims 8, 9, and 38-40

Claims 8, 9 and 38-40 stand rejected as allegedly obvious based on Roche *et al*., (Microbiology 149:643-654, March 2003), in few of Foster *et al.,* (US 2003/0186275)(275). Roche *et al*., is cited for describing a polypeptide having a structure within the description provided by the claims, and demonstrating the polypeptide reacts specifically with antibodies in convalescent sera from patients with *S. aureus* infections; and Foster *et al.,* is cited for the addition of a carrier and/or adjuvant. The Examiner takes the position it would have been *prima facie* obvious to one of ordinary skill in the art to combine the Roche *et al*. SasJ 48-477 fragment with the Foster *et al*. use of a carrier and/or adjuvant. The rejection is respectfully traversed.

Roche *et al.*, fails to provide a reasonable expectation of success that SasJ would be protective, let alone the SasJ 48-477 fragment would be protective. Absent from Roche *et al.*, is any data illustrating the ability of the antigen to provide protection.

Applicants also note the amendment to claim 8 excludes the Roche *et al.,* SasJ 48-477 fragment.

35 U.S.C. § 112, Second Paragraph (Definiteness)

Claim 8 stands rejected as allegedly indefinite. The Examiner indicates the rejection is maintained based on arguments previously presented, and that such arguments address the Applicants prior arguments. The rejection is respectfully traversed.

Applicants have amended the sequence identity provided in claim 8 and made an editorial change to refer to said *S. aureus*. The preamble description of a patient indicates a possible use of the composition. Reference to providing protective immunity against *S. aureus* in the body of the claim refers to a property of the composition consistent with the claim preamble. The skilled artisan reviewing claim and the specification would readily understand the scope of the claim.

35 U.S.C. § 112, Second Paragraph (Definiteness)

The Examiner indicates it is unclear in claim 7 the stability of which polypeptide is facilitated by the one or more additional regions or moieties. The Examiner's position appears to be that claim 7 does not indicate a purified polypeptide, and in those circumstances when other polypeptides are present it is not clear the stability of which polypeptide is enhanced.

Claim 7 indicates the additional region or moiety is joined to an immunogen comprising an amino acid sequence. Reference to amino acid sequence provides for a polypeptide. The skilled artisan reading claim 7 would readily understand the additional region or moiety facilitates stability of the polypeptide it is attached to, which is the only amino acid sequence specifically recited as present.

35 U.S.C. § 112, Second Paragraph (Definiteness)

Claims 9 and 38-54, which depend directly or indirectly from claims 7 or 8, are rejected as allegedly indefinite. The rejection is based on claims 7 and 8 allegedly being indefinite. As discussed above, claim 7 and 8 are not indefinite.

35 U.S.C. § 112, Second Paragraph (Written Description)

Claims 1, 4, 7-9, 33-35, 38-44 and 49-51 stand rejected as allegedly lacking adequate written description support. The Examiner refers to prior arguments and provides some comments. The rejection is respectfully traversed.

Applicants have previously pointed out written description support and addressed the arguments presented by the Examiner. As previously discussed, the present application reasonably conveys to those skilled in the art the inventors had possession of the claimed subject matter as of the filing date by providing representative species of polypeptides within the claimed genus. Representative species of polypeptides are illustrated by the use of SEQ ID NO: 1, and longer-length polypeptides containing a SEQ ID NO 1 region, to provide protection against heterologous challenge strains of *S. aureus*. (Discussed throughout Appeal Brief filed July 23, 2011 (hereinafter "Appeal Brief"), and Appellant Reply Brief filed January 10, 2011 (hereinafter "Reply Brief").

The comments presented by the patent office in the present office action relate to

previous Examiner arguments already addressed by Applicants. Such arguments ignore the teachings provided by the present application to one of ordinary skill in art. The patent office is improperly attempting to limit the claims to exact sequence of tested polypeptide without any considerations as to the expectations of the one of ordinary skill art taking into account the heterologous challenge experiments provided in the application.

The Examiner indicates Applicants state the Office is incorrect in assuming conformational "epitomes" are present. Applicants have made no such assertion. The Examiner's comment appears to be directed to the use of "epitomes," instead of "epitopes". To extent any confusion was caused by reference to "epitomes," instead of "epitopes", Applicants apologize.

Substantively, Applicants did make the assertion indicted by the Examiner. Applicants asserted:

> The Examiner's Answer refers to the patent application indicating that fragments of SEQ ID NO: 2 that provided amino acids 82-486 and 42-196 were not protective. The Office notes the 82-486 fragment has as high as 91% identity to SEQ ID NO: 1 and falls within claim 7. The Office indicates that splitting an active fragment into two inactive pieces raises the possibility of potential conformation protective epitopes, and argues this showing points to the criticality of retaining all amino acid residues.
>
> **Assuming conformational epitomes are present, the Office is incorrect in extrapolating that it is critical to retain all the amino acids of SEQ ID NO: 1 except the N-terminal methionine.** No basis for the necessity of retaining every single amino acid of SEQ ID NO: 1 is provided. (Emphasis added.)

Applicants' comments address the possibility of conformational epitopes and pointed out the extrapolation make by the patent office is not correct.

The Examiner continues to base the rejection on arguments SEQ ID NO: 28 induces death, but indicates it did not include the phrase "cell death" either as such or in connection with SEQ ID NO: 28. The phrase "induces death in an animal model" would have been a more appropriate characterization of the Examiner's prior argument.

Substantively, the Examiner is incorrect in its assertion that SEQ ID NO: 28 induces death. Death in animal models was caused by the *S. aureus* challenge strain, not SEQ ID NO: 28.

In response to prior Applicants comments on data provided in the application illustrating

a difference in survival rates at different days between immunized and non-immunized test animals, the Examiner takes the position that such as delay is not important because the experiment concluded at a later date. Absent from the Examiner's position is a rationale why the skilled artisan would ignore data provided in the application.

The data provided in the application included figures showing the immunogen protective effect at different days, not just at the end of experiment. As pointed out in the application, the provided examples are for illustration purposes and do not limit the claimed invention:

> Examples are provided below further illustrating different features of the present invention. The examples also illustrate useful methodology for practicing the invention. These examples do not limit the claimed invention.

(Application on page 23, lines 30-33.)

The Examiner repeats prior arguments concerning SEQ ID NO: 28 not being within the scope of the claims. Again, the Examiner fails to consider the provided data in context with other data provided in the application. (Discussed throughout the Appeal Brief and Reply Brief.)

The Examiner presents some comments concerning interpretation of claim 7 and fragment 2. The amendment provided to claim 7 structurally excludes fragment 2.

The allegation that fragment 2 not being active demonstrates that each amino acid is critical is not supported by the Examiner. For example, no rationale is provided as to why the inability of a polypeptide 91% identical to SEQ ID NO: 1 means that a polypeptide within 94%, or greater identity would not be protective. As discussed throughout the Appeal Brief and Reply Brief, heterologous data protection provided in the application clearly demonstrates that changes could be made to SEQ ID NO: 1.

Applicants note the § 102 rejection provided to claims 1, 4, 7, 33 and 49, is based on the Roche *et al.* SasJ48-477 fragment inherently being protective. While the exact degree of sequence identity between the SasJ48-477 and SEQ ID NO: 1 is not certain, there are at least 17 amino acid alterations. As noted above, the claims were amended to provide for a greater degree of sequence identity than provided by SasJ48-477, even assuming 100% identity in the region of overlap between the SasJ48-477 and SEQ ID NO: 1.

The Examiner repeats prior arguments concerning the need to show protection in all possible humans against every possible *S. aureus*. As previously explained, the claims are

directed to compounds and compositions. (See, for example, Appeal Brief, at section I.A.5.i, on pages 22 and 23.) The rejection goes to enablement, and enablement can be based on any use. As the rejection appears to be based on enablement for certain uses, Applicants note that: "The enablement requirement is met if the description enables any mode of making and using the claimed invention." *Engel Industries Inc. v. The Lockformer Co.* 946 F.2d 1528**,** 1533, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991).

The Examiner again points to Colman P.M. (*Research Immunol.* 145:33-36, 1994), McGuiness *et al.,* (*Mol. Microbiol.* 7:505-514, Feb 1993), and McGuiness *et al*., (*Lancet* 337:514-517, March 1991) for arguments that a change of a single amino acid can disrupt function. As previously pointed out by the Applicants, the possibility that some alteration in a particular amino acid residue may impact a protein-antibody interaction, does not equate to a significant number of polypeptides within the scope of the claims losing its ability to provide protective immunity if a random amino acid is changed. (See, for example, Appeal Brief, at section I.A.5.j, on pages 23 and 24.)

The possibility of there being a critical amino acid within SEQ ID NO: 1, does not mean every amino acid is critical. The Examiners argument fails to document a basis for a **significant number of polypeptides** within the scope of the claims being inactive. Instead, the cited references concern the possibility of a well placed alteration affecting activity.

The patent office goes on to cite case law and argue that the protective epitopes are not specifically identified and therefore written description is lacking. As pointed out, throughout the Appeal Brief and Reply Brief, such arguments fail to consider the heterologous experiments with SEQ ID NO: 28 and SEQ ID NO: 1 that demonstrate SEQ ID NO: 1 is representative of the claimed genus.

The Examiner provides several comments concerning the Becker sequence and the data obtained with the Becker sequence not being sufficient to establish a correlation between structure and function because the actual sequence was not provided in the application. In the telephone conversation referred to by the Examiner, Applicants' representative indicated that the Becker sequence was not provided in the application. The conversation did not involve the question as to whether Applicants were in possession of the Becker sequence at the time the application was filed.

S. aureus strain Becker is a prior art laboratory strain of *S. aureus*, as opposed to *S. aureus* obtained from a clinical isolate. (See the present application at Table 3 pages 28 and 29.) The present application indicates the ORF0657n strain Becker sequence has a sequence identity to SEQ ID NO: 2 of 95%. (The present application in Table 3, on page 29.) In the region corresponding to SEQ ID NO: 1, Strain Becker ORF0657n has 17 amino acid differences compared to SEQ ID NO: 1. (See Appeal Brief, Exhibit B sequence comparison.)

Reference to percent identity in the application, reasonably conveys to the skilled artisan that Applicants had possession of the strain Becker ORF0657 sequence. If desired, the skilled artisan can readily obtain the strain Becker ORF0657n sequence. Examples of techniques for obtaining the sequence are provided in the application, for example, on pages 24, 27 and 28.

The data provided with Strain Becker further establish SEQ ID NO: 1 is representative of the claimed genus. The absence of the Strain Becker sequence does not take away from results shown in the application demonstrating protection against the heterologous strain Becker.

The Examiner refers to Applicants note of the Office's documentation of inconsistent and non-reproducible protection. It is not clear what is meant by the Examiner's assertion. The protection data observed in the application was reproducible, though the particular level of protection can vary.

The Examiner equates the ability of polypeptide to provide protection with it being **critical** to retain the exact sequence tested. (See for example, Office Action dated 4/13/2011 at page 23.) Such arguments are an attempt to limit the claims to the exact sequence based on the rationale that some undefined alteration, possible one out of the 446 amino acids present in SEQ ID N: 1 may impact polypeptide activity. The possibility of a particular alteration adversely affecting activity does not mean a change to any of the amino acid will result in no activity.

The Examiner in the paragraph number 14, provides comments directed to ". . . prior art made of record and not relied upon in any of the rejections . . .". (Office Action date 4/13/2011 at page 30.) However, some of the references cited therein are relied upon in other parts of the office action (*e.g.,* McGuiness *et al.,* (*Mol. Microbiol.* 7:505-514, Feb 1993), and McGuiness *et al.*, (*Lancet* 337:514-517, March 1991.)

More puzzling is the Examiner's reference to US2006-177462 in paragraph 14. (Office Action dated 4/13/2011 at page 31 and 32.) US2006-177462 is the publication of the current

application. The Examiner is clearly incorrect in its characterization of US2006-177462, including the data provided therein. (See for example, the present response, Appeal Brief, and Reply Brief.)

Please charge deposit account 13-2755 for fees due in connection with this amendment. If any time extensions are needed for the timely filing of the present amendment, Applicants petition for such extensions and authorize the charging of deposit account 13-2755 for the appropriate fees.

Respectfully submitted,

By /Sheldon O. Heber, Reg. No. 38,179/

Sheldon O. Heber
Reg. No. 38,179
Attorney for Applicants

Merck & Co., Inc.
P.O. Box 2000
Rahway, NJ 07065-0907
(732) 594-1958

Exhibit A
Sequence Comparison

```
                1                                                          60
  SEQ2     (1) MNKQQKEFKSFYSIRKSSLGVASVAISTLLLLMSNGEAQAAAEETGGTNTEAQPKTEAVA
  SEQ3     (1) ------------------------------------MAEETGGTNTEAQPKTEAVA
  SEQ1     (1) ------------------------------------MAEETGGTNTEAQPKTEAVA
48-477     (1) ---------------------------------------------TNTEAQPKTEAVA
               61                                                         120
  SEQ2    (61) SPTTTSEKAPETKPVANAVSVSNKEVEAPTSETKEAKEVKEVKAPKETKEVKPAAKATNN
  SEQ3    (21) SPTTTSEKAPETKPVANAVSVSNKEVEAPTSETKEAKEVKEVKAPKETKEVKPAAKATNN
  SEQ1    (21) SPTTTSEKAPETKPVANAVSVSNKEVEAPTSETKEAKEVKEVKAPKETKEVKPAAKATNN
48-477    (14) SPTTTSEKAPETKPVANAVSVSNKEVEAPTSETKEAKEVKEVKAPKETKEVKPAAKATNN
               121                                                        180
  SEQ2   (121) TYPILNQELREAIKNPAIKDKDHSAPNSRPIDFEMKKKDGTQQFYHYASSVKPARVIFTD
  SEQ3    (81) TYPILNQELREAIKNPAIKDKDHSAPNSRPIDFEMKKKDGTQQFYHYASSVKPARVIFTD
  SEQ1    (81) TYPILNQELREAIKNPAIKDKDHSAPNSRPIDFEMKKKDGTQQFYHYASSVKPARVIFTD
48-477    (74) TYPILNQELREAIKNPAIKDKDHSAPNSRPIDFEMKKKDGTQQFYHYASSVKPARVIFTD
               181                                                        240
  SEQ2   (181) SKPEIELGLQSGQFWRKFEVYEGDKKLPIKLVSYDTVKDYAYIRFSVSNGTKAVKIVSST
  SEQ3   (141) SKPEIELGLQSGQFWRKFEVYEGDKKLPIKLVSYDTVKDYAYIRFSVSNGTKAVKIVSST
  SEQ1   (141) SKPEIELGLQSGQFWRKFEVYEGDKKLPIKLVSYDTVKDYAYIRFSVSNGTKAVKIVSST
48-477   (134) SKPEIELGLQSGQFWRKFEVYEGDKKLPIKLVSYDTVKDYAYIRFSVSNGTKAVKIVSST
               241                                                        300
  SEQ2   (241) HFNNKEEKYDYTLMEFAQPIYNSADKFKTEEDYKAEKLLAPYKKAKTLERQVYELNKIQD
  SEQ3   (201) HFNNKEEKYDYTLMEFAQPIYNSADKFKTEEDYKAEKLLAPYKKAKTLERQVYELNKIQD
  SEQ1   (201) HFNNKEEKYDYTLMEFAQPIYNSADKFKTEEDYKAEKLLAPYKKAKTLERQVYELNKIQD
48-477   (194) HFNNKEEKYDYTLMEFAQPIYNSADKFKTEEDYKAEKLLAPYKKAKTLERQVYELNKIQD
               301                                                        360
  SEQ2   (301) KLPEKLKAEYKKKLEDTKKALDEQVKSAITEFQNVQPTNEKMTDLQDTKYVVYESVENNE
  SEQ3   (261) KLPEKLKAEYKKKLEDTKKALDEQVKSAITEFQNVQPTNEKMTDLQDTKYVVYESVENNE
  SEQ1   (261) KLPEKLKAEYKKKLEDTKKALDEQVKSAITEFQNVQPTNEKMTDLQDTKYVVYESVENNE
48-477   (254) KLPEKLKAEYKKKLEDTKKALDEQVKSAITEFQNVQPTNEKMTDLQDTKYVVYESVENNE
               361                                                        420
  SEQ2   (361) SMMDTFVKHPIKTGMLNGKKYMVMETTNDDYWKDFMVEGQRVRTISKDAKNNTRTIIFPY
  SEQ3   (321) SMMDTFVKHPIKTGMLNGKKYMVMETTNDDYWKDFMVEGQRVRTISKDAKNNTRTIIFPY
  SEQ1   (321) SMMDTFVKHPIKTGMLNGKKYMVMETTNDDYWKDFMVEGQRVRTISKDAKNNTRTIIFPY
48-477   (314) SMMDTFVKHPIKTGMLNGKKYMVMETTNDDYWKDFMVEGQRVRTISKDAKNNTRTIIFPY
               421                                                        480
  SEQ2   (421) VEGKTLYDAIVKVHVKTIDYDGQYHVRIVDKEAFTKANTDKSNKKEQQDNSAKKEATPAT
  SEQ3   (381) VEGKTLYDAIVKVHVKTIDYDGQYHVRIVDKEAFTKANTDKSNKKEQQDNSAKKEATPAT
  SEQ1   (381) VEGKTLYDAIVKVHVKTIDYDGQYHVRIVDKEAFTKANTDKSNKKEQQDNSAKKEATPAT
48-477   (374) VEGKTLYDAIVKVHVKTIDYDGQYHVRIVDKEAFTKANTDKSNKKEQQDNSAKKEA----
               481                                                        540
  SEQ2   (481) PSKPTPSPVEKESQKQDSQKDDNKQLPSVEKENDASSESGKDKTPATKPTKGEVESSSTT
  SEQ3   (441) PSKPTPSPVEKESQKQDSQKDDNKQLPSVEKENDASSESGKDKTPATKPTKGEVESSSTT
  SEQ1   (441) PSKPTP------------------------------------------------------
48-477   (430) ------------------------------------------------------------
               541                                                        600
  SEQ2   (541) PTKVVSTTQNVAKPTTASSKTTKDVVQTSAGSSEAKDSAPLQKANIKNTNDGHTQSQNNK
  SEQ3   (501) PTKVVSTTQNVAKPTTASSKTTKDVVQTSAGSSEAKDSAPLQKANIKNTNDGHTQSQNNK
  SEQ1   (447) ------------------------------------------------------------
48-477   (430) ------------------------------------------------------------
               601                                                645
  SEQ2   (601) NTQENKAKSLPQTGEESNKDMTLPLMALLALSSIVAFVLPRKRKN
  SEQ3   (561) NTQENKAKS-----------------------------------
  SEQ1   (447) ---------------------------------------------
48-477   (430) ---------------------------------------------
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